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Serum albumin, cardiometabolic and other adverse outcomes: systematic review and meta-analyses of 48 published observational cohort studies involving 1,492,237 participants

Samuel Seidu[a,b,*], Setor K Kunutsor[c,d], Kamlesh Khunti[a,b]

[a]Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4WP, UK [2]Diabetes

[b]Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4WP, UK

[c]National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK

[d]Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK

***Corresponding author:**

Samuel Seidu, Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4WP, UK; Email: sis11@leicester.ac.uk

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ABSTRACT

Objectives. A general body of evidence suggests that low serum albumin might be associated with increased risk of adverse cardiometabolic outcomes, but findings are divergent. We aimed to quantify associations of serum albumin with the risk of type 2 diabetes (T2D), cardiovascular disease (CVD), all-cause mortality, and other adverse outcomes using a systematic review and meta-analyses of published observational cohort studies. *Design.* MEDLINE, Embase, Web of Science, and manual search of relevant bibliographies were systematically searched to January 2020. Relative risks (RRs) with 95% confidence intervals (CIs) comparing top versus bottom thirds of serum albumin levels were pooled. *Results.* Fifty-four articles based on 48 unique observational cohort studies comprising of 1,492,237 participants were eligible. Multivariable adjusted RRs (95% CIs) comparing the top vs bottom third of serum albumin levels were: 1.03 (0.86-1.22) for T2D; 0.60 (0.53-0.67) for CVD; 0.74 (0.66-0.84) for coronary heart disease (CHD); 0.57 (0.36-0.91) for CHD death; 0.76 (0.65-0.87) for myocardial infarction; 0.66 (0.55-0.77) for all-cause mortality; 0.71 (0.61-0.83) for venous thromboembolism; 0.65 (0.48-0.88) for cancer mortality; and 0.62 (0.46-0.84) for fracture. Heterogeneity between contributing studies of T2D was partly explained by sample sizes of studies (*p* for meta-regression=0.035). *Conclusions.* Elevated levels of serum albumin are associated with reduced risk of vascular outcomes, all-cause mortality, certain cancers, and fracture. Inconsistent findings for T2D may be attributed to selective reporting by studies. Further research is needed to assess any potential causal relevance to these findings and the role of serum albumin concentrations in disease prevention.

Systematic review registration: PROSPERO 2019: CRD42019125869

KEYWORDS

serum albumin; cardiovascular disease; type 2 diabetes; metabolic syndrome; cohort study; systematic review; meta-analysis

Introduction

Serum albumin, a protein which is synthesized in the liver,[1] is a historical marker of nutritional status.[2] Serum albumin has antioxidative properties[3] and low serum concentrations have been suggested to be an indicator of inflammation, hypercoagulable states and liver disease.[4, 5] Serum albumin concentrations have been demonstrated to be inversely correlated with several risk factors for cardiometabolic disease such as age, total cholesterol, body mass index (BMI), and inflammatory markers.[6, 7, 8] Evidence suggests that serum albumin concentrations may be associated with a wide range of cardiometabolic outcomes including cardiovascular disease (CVD),[4, 9, 10] type 2 diabetes,[11, 12] metabolic syndrome,[13, 14], and all-cause mortality.[9] Though the general body of evidence suggests low serum albumin is associated with increased risk of these adverse outcomes; some of the findings have not been consistent. For example, on the relationship between serum albumin and type 2 diabetes; whereas some studies have demonstrated inverse associations,[11, 12] others have reported positive associations,[15] and some others have found no associations.[8, 12] Several reasons could explain the conflicting results and could be related to study design factors such as small sample sizes (low event rates).[15] Furthermore, some previous studies were based on cross-sectional designs,[13, 14] hence the temporal nature of the associations is limited. Though established risk factors explain a large proportion of the risk for these adverse cardiometabolic outcomes, their pathogeneses are still not fully established as it appears other additional factors may be involved. There is therefore a priority to identify and evaluate potentially modifiable risk factors that may have predictive or causal relevance, to help tailor preventive and therapeutic strategies for these conditions. Serum albumin is such a biomarker which has potential promise for the prevention of adverse cardiometabolic outcomes. Given that individual studies are often poorly powered and their results are not always definitive, we sought to quantify the nature, magnitude and specificity of potential longitudinal associations of serum albumin with the risk of adverse cardiometabolic outcomes such as type 2 diabetes, CVD, metabolic syndrome, and all-cause mortality in more detail than ever before using a systematic review and meta-analysis of available observational cohort studies. In subsidiary analyses, we also explored associations with other adverse health outcomes such as venous thromboembolism (VTE), cancer, and fracture outcomes.

Methods

Data sources, searches and screening

This review has been registered in the PROSPERO prospective register of systematic reviews (CRD42019125869). The systematic review and meta-analysis was based on a predefined protocol and conducted in accordance with PRISMA and MOOSE guidelines [16, 17] (**Supplementary Tables 1-2**). MEDLINE and Embase were searched from inception to 30 January 2020. The computer-based searches used a combination of MeSH terms related to the exposure (e.g., serum albumin) and outcomes (e.g., cardiovascular disease, type 2 diabetes, mortality) in humans with no language restrictions. The detailed search strategy is reported in **Supplementary Table 3**. The titles and abstracts of citations identified from the databases were then initially screened to identify articles potentially eligible for inclusion. Following this, full texts of relevant articles were acquired for further evaluation. The full text evaluation was independently conducted by two authors (SKK and SS) based on the inclusion criteria indicated below. Any disagreements regarding eligibility of an article was discussed, with involvement of a third author when necessary (KK). Reference lists of relevant studies and the "cited by" function in Web of Science were assessed to identify additional studies missed by the search strategy.

Eligibility criteria

Studies were included if they met the following search criteria: were population-based observational (prospective or retrospective cohort, case cohort, or nested case-control) in design; had sampled from healthy (i.e., were based on initially healthy participants) or general populations (ie, populations with both healthy and prevalent cases of cardiometabolic disease at baseline); had evaluated the associations of circulating albumin concentrations with primary and secondary outcomes; and had at least one year of follow-up. The primary outcomes were cardiometabolic outcomes and included CVD (including cardiovascular endpoints such as coronary heart disease (CHD), myocardial infarction (MI), and stroke), type 2 diabetes, metabolic syndrome, and all-cause mortality. Secondary outcomes were other cardiometabolic and nonvascular outcomes including hypertension, heart failure, venous thromboembolism, dementia, cancer and fracture. We excluded studies for the following reasons: (i) they only reported on mean levels and standard deviations of serum albumin in cases and non-cases; (ii) were based exclusively in participants with pre-existing cardiometabolic disease; or (iii) were case-control, cross-sectional or ecological in design.

Data extraction and quality assessment

One author (SKK) initially extracted data from eligible studies using a standardized predesigned data collection form, which has been used in previous similar reviews.[18, 19] A second author (SS) independently checked the extracted data with that in original articles. Data were extracted for the following study characteristics: author and year of publication, country of study, baseline year of study, study design, age, sex, assay type, type of outcome, sample size and number of outcomes, duration of follow-up, degree of adjustment for potential confounders [defined as '+' (when risk estimates were adjusted for age and/or sex); '++' (further adjustment for established risk factors such as smoking status, body mass index, blood pressure, lipids); and '+++' (additional adjustment for emerging risk factors such as inflammatory markers)], and risk estimates reported for greatest adjustment for potential confounders. To avoid double counting of participants within a study cohort, study selection was limited to a single set of comprehensive information when there were several publications involving the same study cohort. Selection was based on the study with the most up-to-date information (longest follow-up duration and/or analysis covering the largest number of participants). Methodological quality of studies was assessed using the nine-star Newcastle–Ottawa Scale (NOS),[20] which uses pre-defined criteria namely: selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome. Nine points on the NOS reflects the highest study quality.

Data synthesis and analysis

Summary measures of associations were presented as relative risks (RRs) with 95% confidence intervals (CIs). To enable consistency in the pooling approach and enhance interpretation of the findings, RR estimates for the associations of serum albumin and outcomes were transformed to consistently correspond to the comparison of the top versus bottom third of the distribution of serum albumin levels in each study, using standard statistical methods previously described [19, 21] (**Supplementary Table 4**). Briefly, log risk estimates were transformed assuming a normal distribution (or that a transformation of the exposure variable for which the risk ratio is based was normally distributed), with the comparison between top and bottom thirds being equivalent to 2.18 times the log risk ratio for a 1 standard deviation increase (or equivalently, as 2.18/2.54 times the log risk ratio for a comparison of extreme quarters and as 2.18/2.80 times the log risk ratio

for a comparison of extreme quintiles). Standard errors of the log risk estimates were calculated using reported confidence intervals and were standardised in the same way. For estimates that could not be transformed, the top versus bottom categories were used as reported in the included studies. We have shown that pooled estimates from transformed and untransformed data are qualitatively similar.[22] When the highest quantile (eg, top third) was used as the referent, we converted the reported risk estimate into its reciprocal. When studies reported more than one estimate of an association according to subgroups (e.g., by sex), a within-study summary estimate was calculated using a fixed effect meta-analysis. Random-effects models were used to combine RRs to account for the effect of heterogeneity.[23] Heterogeneity between studies was assessed using the standard χ^2 statistic and the I^2 statistic.[24] We assessed heterogeneity between cohorts by comparing results from studies grouped according to prespecified study level characteristics such as geographical location, sex, average age at baseline, average duration of follow-up, number of outcomes recorded, degree of statistical adjustment, and study quality using random effects meta-regression.[25] We assessed for evidence of publication bias using visual inspection of Begg's funnel plots[26] and Egger's regression symmetry tests.[27] All analyses were conducted using Stata MP 16 (Stata Corp, College Station, Texas, USA).

Results

Study identification and selection

The study selection process is illustrated in **Figure 1**. The initial search as well as the manual screening of relevant citations identified 2,886 potentially relevant citations. After screening of citations based on titles and abstracts, 77 citations were selected for full text evaluation. A total of 23 articles were excluded because (i) exposure was not relevant (n=11); (ii) study design not relevant (n=4); (iii) duplicate of a previous publication using the same cohort (n=4); (iv) outcome not relevant (n=3); and (v) risk estimates could not be calculated (n=1). In total, we included 54 articles based on 48 unique observational cohort studies.[5, 6, 8, 9, 10, 11, 12, 15, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73]

Study characteristics and quality

Table 1 summarizes characteristics and quality assessment scores of each of the eligible studies evaluating the associations between serum albumin and risk of several outcomes. Publication dates of eligible studies ranged from 1990 to 2020. Overall, the 48 unique cohorts comprised of 1,492,237 participants. The majority of studies were based on prospective cohort designs (n=37), with the remainder based on retrospective cohort (n=4), nested case-control (n=4), and case-cohort (n=3) designs. Overall, 19 studies were conducted in North America (USA), 17 in Europe (Austria, Finland, France, Germany, Netherlands, Norway, Russia, Spain, Sweden, and UK), and 12 in Asia (China, Japan, Korea, and Taiwan). Overall, the average baseline age of participants in the included studies ranged from 37.6 to 97.0 years and the weighted mean age was 50.9 years. The average overall duration of follow-up for outcomes ranged from 1.0 to 28.5 years, with a weighted mean follow-up duration of 8.8 years. For studies providing these data, the overall average serum albumin level ranged from 37.3 to 51.0 g/l with a weighted mean of 42.7 g/l. The overall methodological quality scores of studies using NOS ranged from 5 to 9.

Serum albumin and risk of primary outcomes

Figure 2 provides a summary of meta-analyses of the associations between serum albumin and risk of the primary and secondary outcomes evaluated. In meta-analysis of 9 studies,[8, 11, 12, 15, 54, 66, 68, 73] comparing the top versus bottom third of serum albumin levels, the pooled fully-adjusted RR (95% CI) of type 2 diabetes was 1.03 (0.86-1.22) (**Figure 3**). There was significant heterogeneity between contributing studies (I^2 =68%; 95% CI 33, 85%; *p for heterogeneity*<0.001), which seemed to be partly explained by the sample size (*p* for meta-regression=0.04). Smaller studies were more likely to report more extreme results compared with larger studies (**Supplementary Figure 1**). In meta-analyses of cardiovascular outcomes, RRs (95% CIs) were 0.60 (0.53-0.67; I^2 =22%; 95% CI 0, 66%; *p* for heterogeneity=0.27, n=6 studies[38, 42, 52, 62, 71, 74]) for CVD; 0.74 (0.66-0.84; I^2 =59%; 95% CI 5, 82%; *p for heterogeneity*=0.02, n=7 studies[10, 30, 35, 38, 42, 69, 74]) for CHD; 0.57 (0.36-0.91; I^2 =51%; 95% CI 0, 86%; *p for heterogeneity*=0.13, n=3 studies[30, 35, 38]) for CHD mortality; 0.76 (0.65-0.87; I^2 =0%; 95% CI 0, 85%; *p for heterogeneity* =0.59, n=4 studies[9, 30, 48, 58]) for MI; and 0.99 (0.60-1.63; I^2 =91%; 95% CI 75, 96%; *p for heterogeneity*<0.001, n=3 studies[33, 42, 58]) for stroke comparing top versus bottom thirds of serum albumin levels (**Figure 2; Supplementary Figure 2**). Comparing the top versus bottom thirds of serum albumin levels in 21 studies, the

pooled RR (95% CI) for all-cause mortality was 0.65 (0.55-0.77) with substantial heterogeneity between contributing studies (I^2 =97%; 95% CI 96, 97%; *p for heterogeneity*<0.001) (**Figure 4**), which seemed to be explained partly by the duration of follow-up (*p* for meta-regression=0.023). The association was stronger for studies with shorter follow-up duration (<10 years) compared with studies of longer follow-up duration (≥10 years) (**Supplementary Figure 3**). In meta-analysis of 3 studies that compared hypoalbuminaemia versus normal albumin,[37, 43, 50] the RR (95% CI) for all-cause mortality was 1.31 (0.86-1.98; I^2 =67%; 95% CI 0, 91%; *p for heterogeneity*=0.05) (**Supplementary Figure 4**). Results from single reports showed a decreased risk of ischaemic stroke,[58] SCD,[48] and non-SCD[48] comparing the top versus bottom tertile of serum albumin levels; whereas the risk of MetS[60] and stroke mortality[33] was increased (**Supplementary Figure 5**). Three studies could not be included in the pooled analyses due to the inconsistent reporting of and lack of complete data on risk estimates.[29, 45, 64] Darne et al.[29] in their report published in 1990, showed that serum albumin was not significantly associated with cardiovascular, cancer, and all-cause mortality. In the prospective study of the associations of biomarkers of inflammation and malnutrition with the risk of death in health elderly people, Carriere and colleagues showed that low serum albumin was associated with early death in men; no associations were demonstrated for women.[45] In patients without pre-existing cardiovascular diagnoses, Hayward and colleagues demonstrated low serum albumin to be associated with an increased risk of cardiac events.[64]

Serum albumin and risk of secondary outcomes

In meta-analysis of 4 studies,[5, 6, 57] comparing the top versus bottom third of serum albumin levels, the pooled RR (95% CI) of VTE was 0.71 (0.61-0.83; I^2 =0%; 95% CI 0, 85%; *p for heterogeneity*=0.41) (**Figure 2; Supplementary Figure 6**). In meta-analyses of cancer endpoints, RRs (95% CIs) were 0.65 (0.48-0.88, I^2 =79%; 95% CI 44, 92%; *p for heterogeneity*=0.003, n=4 studies[42, 62, 65, 71]) for cancer mortality and 0.92 (0.85-1.00, I^2 =0%; 95% CI 0, 0%; *p for heterogeneity*=0.76, n=3 studies[39, 63, 65]) for colorectal cancer comparing top versus bottom thirds of serum albumin (**Supplementary Figure 7**). The corresponding RR (95% CI) for fracture in meta-analysis of two studies[36, 72] was 0.62 (0.46-0.84) (**Supplementary Figure 8**). Findings from single reports showed a decreased risk of heart failure,[49] hypertension,[56] breast cancer,[65] colorectal cancer death,[63] and colon cancer;[34] an increased risk of ovarian cancer[67] and no

significant associations with all-cause cancer,[38] lung cancer,[65] and prostate cancer[65] (**Supplementary Figure 8**). In single studies that compared hypoalbuminaemia with normal albumin levels, the risk was increased for heart failure,[50] cancer,[61] and mild cognitive impairment[70] (**Supplementary Figure 9**).

Publication bias

Though tests of publication bias have low power and are unreliable in meta-analysis involving <10 studies,[75] we assessed for publication bias among studies of type 2 diabetes as the results of the subgroup analysis suggested evidence of selective reporting (small study effects) (**Supplementary Figure 1**). There was no evidence of publication bias across studies of type 2 diabetes, with the funnel plot showing no evidence of asymmetry (**Supplementary Figure 10**) and Egger's test for bias giving a *p*-value of 0.72. A funnel plot of the 21 studies reporting on the associations between serum albumin and all-cause mortality risk showed visual evidence of symmetry (**Supplementary Figure 10**) which was consistent with Egger's regression symmetry test (p=0.34). We also found no evidence of such selective reporting when studies were grouped by sample size in meta-regression analysis (i.e., results were similar for smaller and larger studies) (**Supplementary Figure 3**).

Discussion

Key findings

These meta-analyses on the associations between serum albumin and several adverse outcomes indicates that elevated circulating levels of serum albumin in approximately healthy people are associated with reduced risk of CVD endpoints (including composite CVD, CHD, MI, SCD, and heart failure), all-cause mortality, hypertension, VTE, cancer mortality, breast cancer, colon cancer, colorectal cancer, and fracture. The risk was however increased for MetS and ovarian cancer. There were no significant associations with type 2 diabetes, lung cancer, and prostate cancer. The association of serum albumin with type 2 diabetes seemed to be modified by sample size; smaller studies were more likely to report more extreme results compared with larger studies, though the associations were not significant. Furthermore, our findings suggested that the association between serum albumin and all-cause mortality risk may be modified by the duration of follow-up, with stronger associations being observed for shorter follow-up durations.

Comparison with previous work

In a previous meta-analysis published over two decades ago, Danesh and colleagues demonstrated low levels of serum albumin to be associated with increased risk of CHD in pooled analysis of eight studies. To our knowledge, this review represents the first comprehensive evaluation of aggregate observational cohort data on the associations of serum albumin with several cardiometabolic and other adverse health outcomes. Being the first attempt at doing this, these findings cannot directly be compared to previous work. Though generally mounting evidence has suggested that low levels of serum albumin are associated with increased risk of cardiometabolic outcomes such as type 2 diabetes, MetS, and CVD (and vice versa), the evidence has been inconsistent in the absence of meta-analyses of the existing data. The current study therefore establishes robust observational associations of serum albumin with the risk of several adverse outcomes.

Possible explanations for findings

Several plausible biological pathways might underlie some of the associations demonstrated. It is well established that inflammatory processes are involved in the aetiopathogenesis of vascular disease.[76, 77] Indeed, several "downstream" and "upstream" markers of inflammation such as C-reactive protein (CRP), fibrinogen, interleukins, and tumour necrosis factor alpha (TNF-α) have been demonstrated to be associated with the risk of CHD.[78, 79, 80] Serum albumin is a negative acute phase reactant and is synthesized by the liver. In the presence of systemic inflammation, there is hepatic synthesis of other acute-phase proteins rather than serum albumin.[81] Hence, it has been suggested that low serum albumin levels may reflect inflammatory states,[5] which underlie the pathogenesis of vascular disease. Since an inflammatory hypothesis has also been postulated in the development of VTE[82] and other outcomes such as all-cause mortality, hypertension, cancer, and fracture,[83] these same inflammatory processes may explain the observational relationships observed. However, since some of the observed associations between serum albumin and outcomes were independent of inflammatory markers such as CRP, interleukins, and TNF-α, it is likely that other pathways may be involved apart from inflammation. Low serum albumin may be a marker of a hypercoagulable state[5] and an indicator of health conditions such as liver disease, nephrotic syndrome, and malignancy, which increase the risk of VTE.[84, 85, 86, 87] Low serum albumin is also an indicator of poor

nutrition,[2] functional decline,[88, 89, 90] and frailty,[37, 91] which all predispose to an increased risk of fractures. Oxidative stress, insulin resistance, and endothelial dysfunction in addition to inflammation, have been implicated in the development of hypertension; [92, 93] serum albumin has antioxidant properties[94] and also inhibits endothelial apoptosis,[95] hence high levels of serum albumin may protect against the development of hypertension. The potent antioxidant activity of serum albumin may contribute to its protective role on cancer risk. There were differential effects of albumin levels on the risk of site-specific cancers, which may reflect the fact that different types of cancer do not have the same pathogenic process. Whether higher serum albumin predisposes to an increased risk of MetS and ovarian cancer or is a marker of these adverse outcomes is unclear. The increased risk of ovarian cancer associated with increased serum albumin is unexpected given that ovarian cancer is associated with low serum albumin levels.[96] Schwartz and colleagues[67] speculate that elevated serum albumin could increase ovarian cancer risk by delivering higher levels of hormones to ovarian tissue, since steroid hormones in blood are bound to albumin. The authors also report that these findings may reflect increased albumin synthesis by ovarian cells.[67] With the inconsistent findings reported for the association between serum albumin and type 2 diabetes in individual studies, pooled analysis showed no evidence of an association. These findings were unexpected given the plausible pathways underlying the associations between serum albumin and adverse cardiometabolic outcomes, which suggest that serum albumin might reduce the risk of type 2 diabetes. Indeed, two of the included studies evaluated the associations between serum albumin change during follow-up and type 2 diabetes risk and observed that an increase in serum albumin during follow-up reduces the risk of type 2 diabetes.[68, 73] Though there was no evidence of publication bias using formal tests, subgroup analyses suggested the current findings might due to selective reporting of studies (small study effects). It is well established that due to ageing, changes in lifestyle, chronic disease, and errors in exposure assessments, using baseline measurements of an exposure could underestimate the true strength of an association between an exposure and disease outcome due to the phenomenon of regression dilution bias.[97] Since our analyses were based on baseline serum albumin concentrations, the pooled estimates could be underestimates. In addition, given the substantial heterogeneity between contributing studies for type 2 diabetes which may be explained by factors such as differences in population characteristics (race, sex, genetic background, and underlying subclinical disease) and study design characteristics (blood sampling, assays for serum albumin measurement,

or confounder adjustment), these findings need careful interpretation and replication in future studies. Finally, evidence of effect modification by follow-up duration on the serum albumin-mortality association might reflect protein degradation between sample collection and assay measurements for serum albumin. Serum samples for determination of albumin were stored at low temperatures (-20℃ or less) for several years by some of the studies and this could have affected the recovery rates of albumin.

Implications of findings

Although the associations demonstrated do not establish causality for any of the outcomes assessed, the comprehensive evaluation helps to bridge the gaps in translating basic scientific findings into clinical practice. Serum albumin is a simple, standardised, cost-effective and scalable biomarker which may represent a potential therapeutic target for the prevention of adverse cardiometabolic outcomes – increasing or avoiding low serum albumin levels could be a strategy for reducing the risk of these health outcomes. A number of randomized controlled trials in surgery have demonstrated that nutritional supplementation is associated with reduced risk of complications such as fracture.[98, 99] Studies are needed to ascertain if the current findings have any causal relevance (Mendelian randomization) and definitive trials are also needed to investigate potential therapeutic implications of albumin supplementation.

Strengths and limitations

This study has several strengths. This represents the first attempt at summarising the overall evidence on the associations of serum albumin with multiple outcomes using meta-analyses. We only included studies that had exclusively recruited participants from general populations, thereby potentially minimizing any 'reverse-causation' effects of clinically evident pre-existing disease on serum albumin levels. Though there was inconsistent reporting of risk comparisons by included studies, we were able to standardise and harmonise risk estimates to a common scale (extreme tertiles) to ensure consistency in the pooling approach. Other strengths included assessment of exploration of heterogeneity and evaluation for publication bias where possible. Our review also had potential limitations. First, some of the findings were based on single or limited number of reports and hence require replication in future studies. Second, we were unable to perform consistent

multivariate adjustments by combining models with the same set of potential confounders owing to the reliance on published data with variable degrees of adjustments across eligible studies. Third, we were unable to correct the estimates for within-person variation in serum albumin levels over time which may have underestimated associations, because the majority of studies evaluated associations using baseline levels of serum albumin. It has been reported that serum albumin may exhibit low within-individual variation (the correlation coefficient between measured levels of serum albumin several years apart is approximately 0.70 [1]); however, studies with repeat assessments of serum albumin are still needed to assess its variability in greater detail. Fourth, given the substantial heterogeneity between contributing studies for some of the outcomes (type 2 diabetes and all-cause mortality), it was arguable whether a summary risk estimate should be presented rather than reporting estimates in relevant subgroups. The presence of substantial heterogeneity makes pooling of risk estimates somewhat controversial; however, in addition to the summary risk estimate, we have also reported risk estimates for the several subgroups assessed although little of the heterogeneity was explained by any of these study characteristics.

Conclusion

This aggregate systematic review and meta-analyses of long-term observational cohort studies involving apparently healthy adults shows that elevated levels of circulating serum albumin are associated with reduced risk of vascular disease, all-cause mortality, hypertension, VTE, certain cancers, and fracture. Inconsistent findings for type 2 diabetes may be attributed to selective reporting by studies. Further research is needed to assess any potential causal relevance to some of these findings and the role of serum albumin concentrations in disease prevention.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Figure legends

Figure 1. PRISMA flow diagram

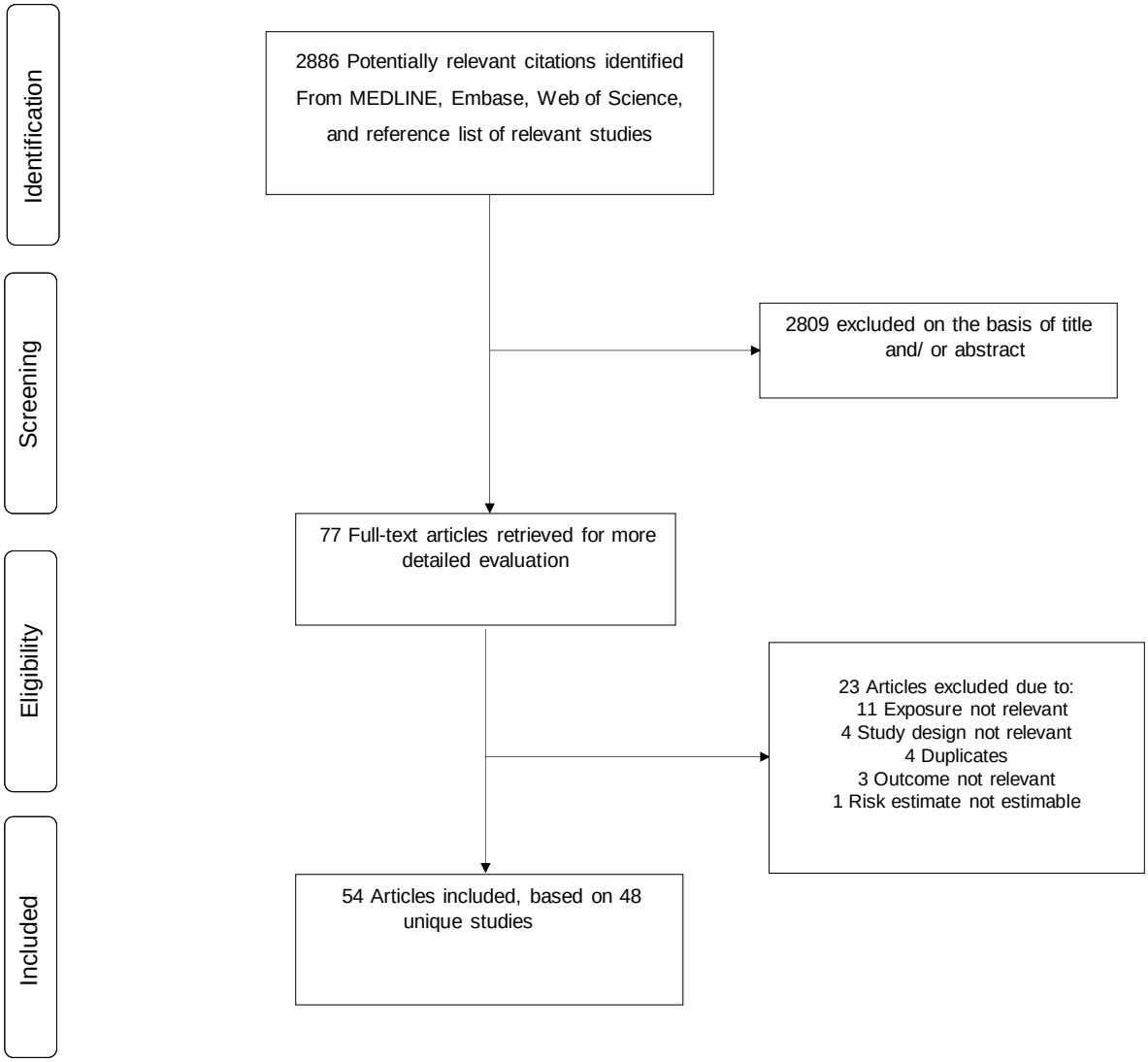
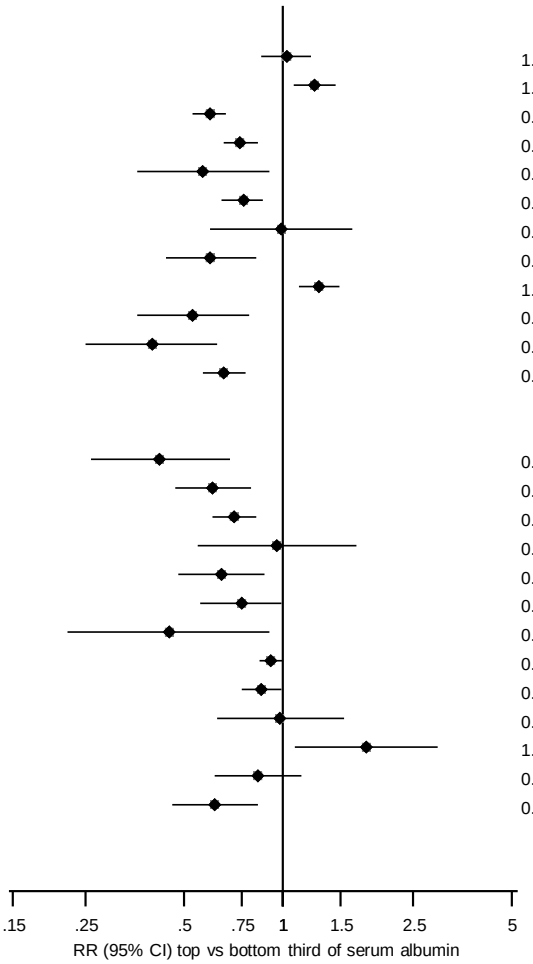


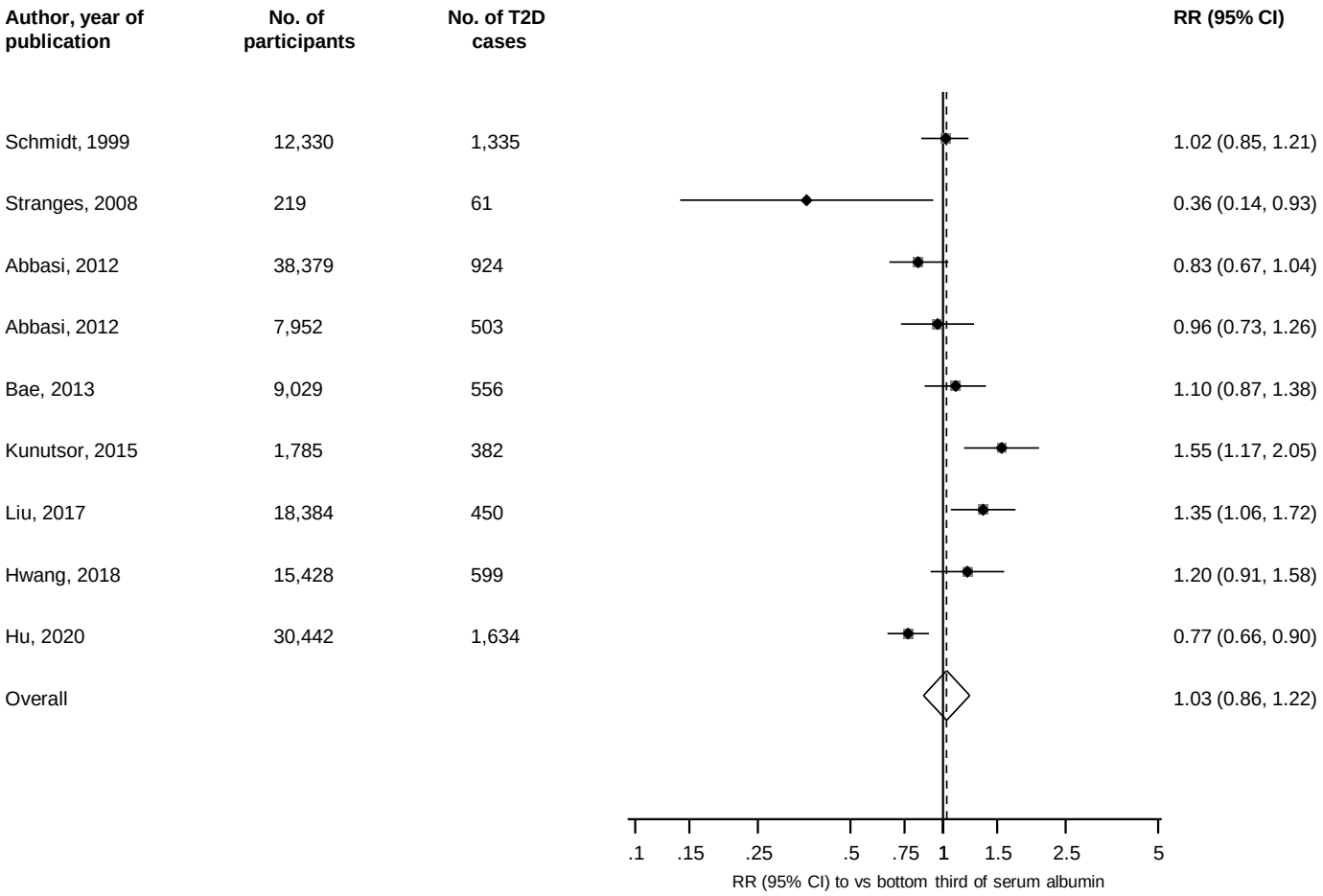
Figure 2. Summary associations of serum albumin with primary and secondary outcomes

Outcome	No. of studies	No. of participants	No. of events	RR (95% CI)	I^2 (95% CI)
Primary outcomes					
Type 2 diabetes	9	133,948	6,444	1.03 (0.86, 1.22)	78 (58 to 88)
Metabolic syndrome	1	12,567	2,582	1.25 (1.08, 1.45)	
CVD	6	97,415	3,176	0.60 (0.53, 0.67)	22 (0 to 66)
Coronary heart disease	7	32,546	3,771	0.74 (0.66, 0.84)	59 (5 to 82)
CHD mortality	3	5,551	412	0.57 (0.36, 0.91)	51 (0 to 86)
MI	4	22,082	1,131	0.76 (0.65, 0.87)	0 (0 to 85)
Stroke	3	15,573	1,268	0.99 (0.60, 1.63)	91 (75 to 96)
Ischemic stroke	1	2,986	271	0.60 (0.44, 0.83)	
Stroke mortality	1	4,897	165	1.29 (1.12, 1.49)	
SCD	1	13,975	207	0.53 (0.36, 0.79)	
Non-SCD	1	13,975	174	0.40 (0.25, 0.63)	
All-cause mortality	21	751,867	68,455	0.66 (0.57, 0.77)	97 (96 to 97)
Secondary outcomes					
Heart failure	1	2,907	342	0.42 (0.26, 0.69)	
Hypertension	1	2,240	331	0.61 (0.47, 0.80)	
Venous thromboembolism	4	53,115	1,013	0.71 (0.61, 0.83)	0 (0 to 85)
All-cause cancer	1	820	65	0.96 (0.55, 1.68)	
Cancer mortality	4	92,258	2,814	0.65 (0.48, 0.88)	79 (44 to 92)
Breast cancer	1	5,132	627	0.75 (0.56, 0.99)	
Colon cancer	1	236	118	0.45 (0.22, 0.91)	
Colorectal cancer	3	331,196	5,197	0.92 (0.85, 1.00)	0 (0 to 0)
Colorectal cancer death	1	4,764	1,466	0.86 (0.75, 0.99)	
Lung cancer	1	5,132	195	0.98 (0.63, 1.54)	
Ovarian cancer	1	404	202	1.80 (1.09, 2.97)	
Prostate cancer	1	5,132	554	0.84 (0.62, 1.14)	
Fracture	2	4,758	251	0.62 (0.46, 0.84)	



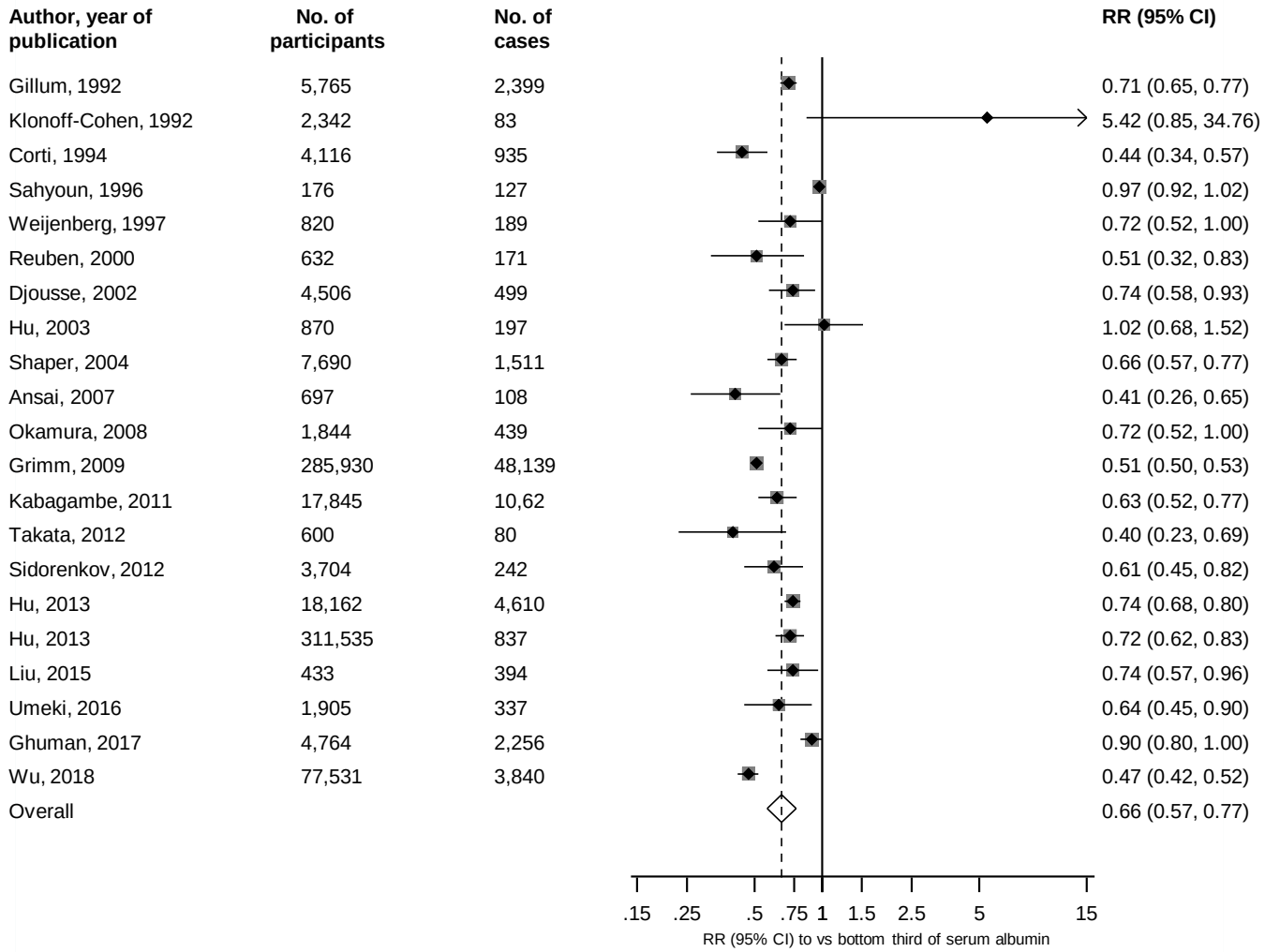
CHD, coronary heart disease; CI, confidence interval (bars); CVD, cardiovascular heart disease; MI, myocardial infarction; RR, relative risk; SCD, sudden cardiac death; VTE, venous thromboembolism

Figure 3. Associations of serum albumin with type 2 diabetes risk in eligible studies



The summary estimates presented were calculated using random effects models; CI, confidence interval (bars); RR, relative risk; T2D, type 2 diabetes

Figure 4. Associations of serum albumin with all-cause mortality risk in eligible studies



The summary estimates presented were calculated using random effects models; CI, confidence interval (bars); RR, relative risk

SUPPLEMENTAL MATERIAL

Supplementary Table 1: PRISMA 2009 check-list

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	None
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary Table 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Results, Figure 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figure 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Results; Table 1
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Results
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion

Section/topic	Item No	Checklist item	Reported on page No
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Discussion

Supplementary Table 2: MOOSE checklist

Serum albumin, cardiometabolic and other adverse outcomes: systematic review and meta-analyses of 48 published observational cohort studies involving 1,492,237 participants

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	A general body of evidence suggests that low serum albumin might be associated with increased risk of adverse cardiometabolic outcomes, but some of the findings are divergent.
√	Hypothesis statement	Serum albumin is associated with risk of several cardiometabolic outcomes and other nonvascular outcomes
√	Description of study outcomes	Primary outcomes: Cardiovascular disease (CVD), type 2 diabetes, metabolic syndrome, and all-cause mortality. Secondary outcomes: Hypertension, heart failure, venous thromboembolism, dementia, cancer and fracture.
√	Type of exposure	Serum albumin
√	Type of study designs used	Observational cohort (prospective or retrospective cohort, case-cohort or "nested case control") population-based studies
√	Study population	Approximately general populations (i.e., did not select participants on the basis of confirmed pre-existing medical conditions such as hypertension, cardiovascular disease, liver disease, or chronic kidney disease at baseline).
Reporting of search strategy should include		
√	Qualifications of searchers	Setor Kunutsor, MD PhD; Samuel Seidu, MD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception of MEDLINE, EMBASE, Web of Science to 30 January 2020. **Search strategy:** Supplementary Table 3
√	Databases and registries searched	MEDLINE, EMBASE, and Web of Science
√	Search software used, name and version, including special features	Ovid was used to search EMBASE Reference Manager used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language
√	Method of handling abstracts and unpublished studies	None found
√	Description of any contact with authors	We contacted authors for more information and data on relative risk estimates and risk comparisons
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels, and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality

	on possible predictors of study results	indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Heterogeneity of the studies was explored with I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods. We performed random effects meta-analysis with Stata MP 16.
√	Provision of appropriate tables and graphics	Table 1, Figures 1-4, Supplementary Materials
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2-4
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Sensitivity analysis was conducted to assess the influence of each individual study by omitting one study at a time and calculating a pooled estimate for the remainder of the studies. Results section
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussed in the context of the results.
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	Future studies to replicate results of single reports
√	Disclosure of funding source	Primary Care Diabetes Europe (PCDE)

Supplementary Table 3: MEDLINE search strategy

Relevant studies, published before 30 January 2020 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, and the Science Citation Index databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), by hand searching of relevant journals and by correspondence with study investigators.

1 exp Serum Albumin/ (79909)
2 exp Cardiovascular Diseases/ (2301627)
3 exp Coronary Disease/ (212416)
4 exp Stroke/ (125186)
5 exp Myocardial Infarction/ (170626)
6 exp Death, Sudden, Cardiac/ (14820)
7 exp Diabetes Mellitus, Type 2/ (124886)
8 exp Metabolic Syndrome/ (29851)
9 exp Dementia/ (157281)
10 exp Mortality/ (364632)
11 exp Death/ (144169)
12 exp Neoplasms/ (3214220)
13 exp Venous Thromboembolism/ (9655)
14 exp Pulmonary Embolism/ (37773)
15 fracture.mp. (193505)
16 exp Hypertension/ (247352)
17 exp Heart Failure/ (115544)
18 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab. (2449135)
19 2 or 3 or 4 or 5 or 6 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (5938267)
20 1 and 18 and 19 (2086)
21 limit 20 to humans (2061)

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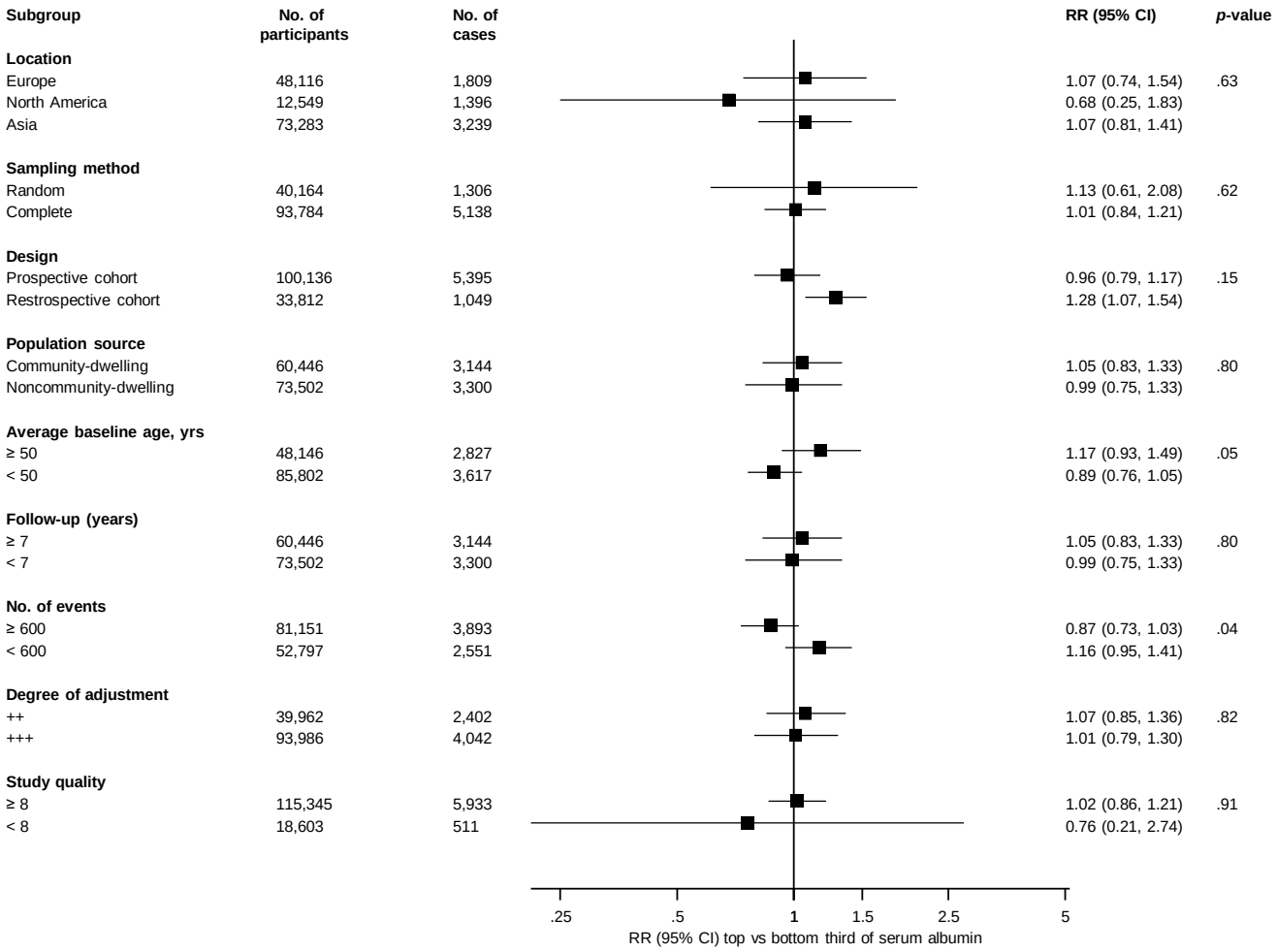
Each part was specifically translated for searching alternative databases.

Supplementary Table 4: Risk conversion method

To enable a consistent approach to the meta-analysis and enhance interpretation of findings, relative risk estimates for association of serum albumin and outcomes that were often differently reported by each study [e.g. per unit or standard deviation (SD) change, quintiles, quartiles, or other groupings] were transformed to involve comparisons between the top third and bottom third of each study population's baseline distribution of serum albumin levels using standard statistical methods.[1,2] Briefly, assuming a normally distributed exposure (e.g. serum albumin) with a linear association with type 2 diabetes risk (i.e. linear relationship between log relative risk estimates and levels of the exposure), conversion factors to convert log relative risks from reported scale comparisons to top versus bottom third comparisons are derived based on the ratio of expected differences in mean levels of the standardised exposure (i.e. SD scale), for the target comparison versus reported comparison. For example, the expected difference in means of the top versus bottom thirds of the standard normal distribution is 2.18 SDs, 2.54 SDs for the top versus bottom quartile, and 2.80 SDs for the top versus bottom quintile. Hence, relative risk estimates reported for comparisons of extreme quartiles can be converted to comparisons of extreme thirds by applying a multiplication conversion factor of 2.18/2.54 to the log relative risk and its standard error and estimates reported for comparisons of extreme quintiles can be converted to comparisons of extreme thirds by applying a multiplication conversion factor of 2.18/2.80 to the estimates. Similarly, estimates reported per 1 SD can be multiplied by 2.18 to obtain the top versus bottom third comparison, and those reported per unit change can be multiplied by 2.18*SD of exposure, to obtain similar comparison. Conversion factors for other possible reported comparisons are derived similarly. The method has been used in previous numerous published meta-analyses.[3-5]

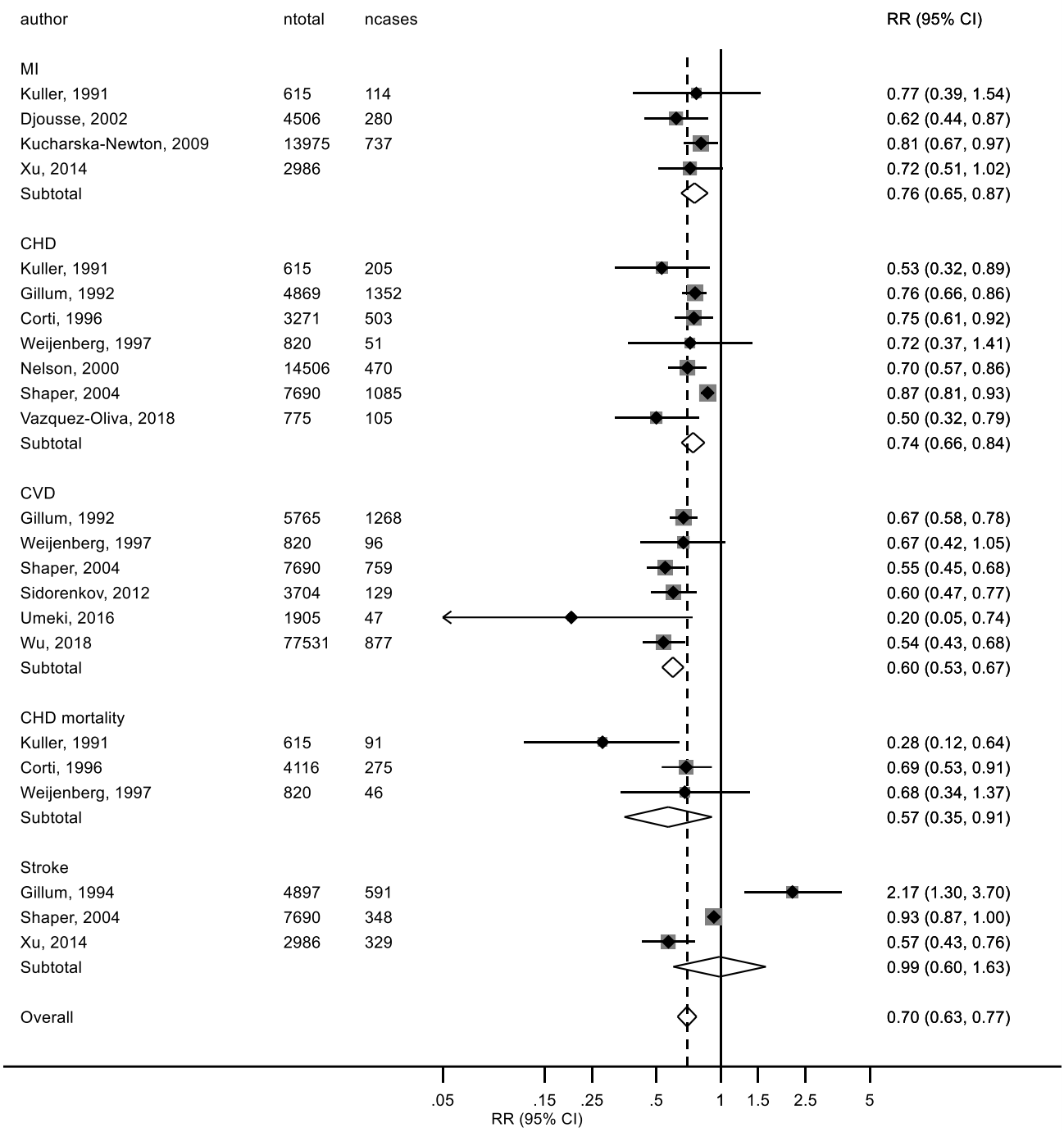
1. Chêne, G and Thompson, SG. Methods for Summarizing the Risk Associations of Quantitative Variables in Epidemiologic Studies in a Consistent Form. American Journal of Epidemiology. 1996;144:610-621
2. Greenland, S and Longnecker, MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American Journal of Epidemiology. 1992;135:1301-1309.
3. Thompson A and Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. J Intern Med. 2006;259:481-492
4. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. BMJ. 2012;345:e6698.
5. Kunutsor SK, Apekey TA, Walley J. Liver aminotransferases and risk of incident type 2 diabetes: a systematic review and meta-analysis. Am J Epidemiol. 2013; 178 (2): 159-17

Supplementary Figure 1: Relative risks for type 2 diabetes in individuals in the top versus bottom thirds of baseline levels of serum albumin, grouped according to study level characteristics



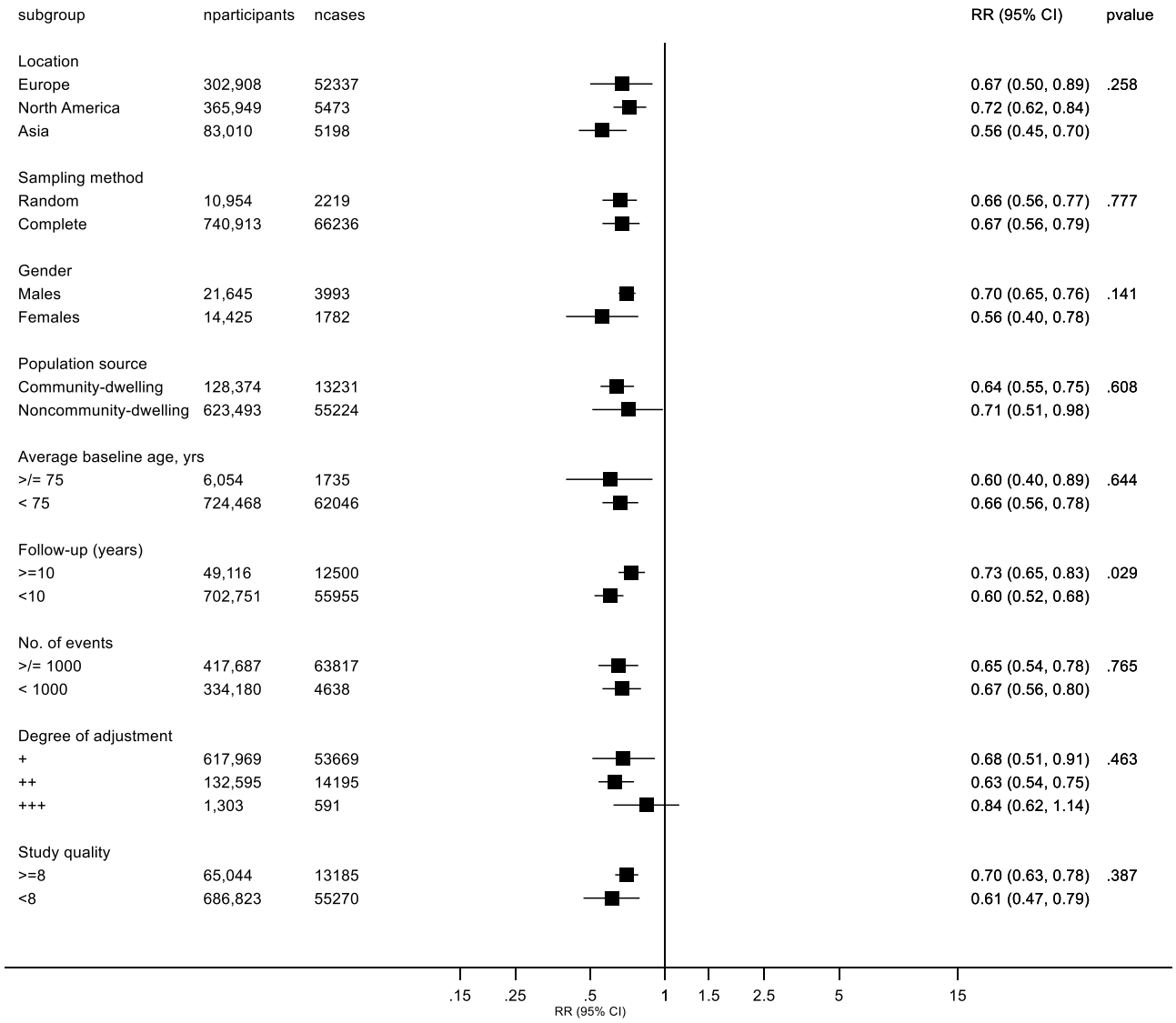
CI, confidence interval (bars); RR, relative risk; p-values are for meta-regression

Supplementary Figure 2: Relative risks for cardiovascular outcomes in individuals in the top versus bottom thirds of baseline levels of serum albumin



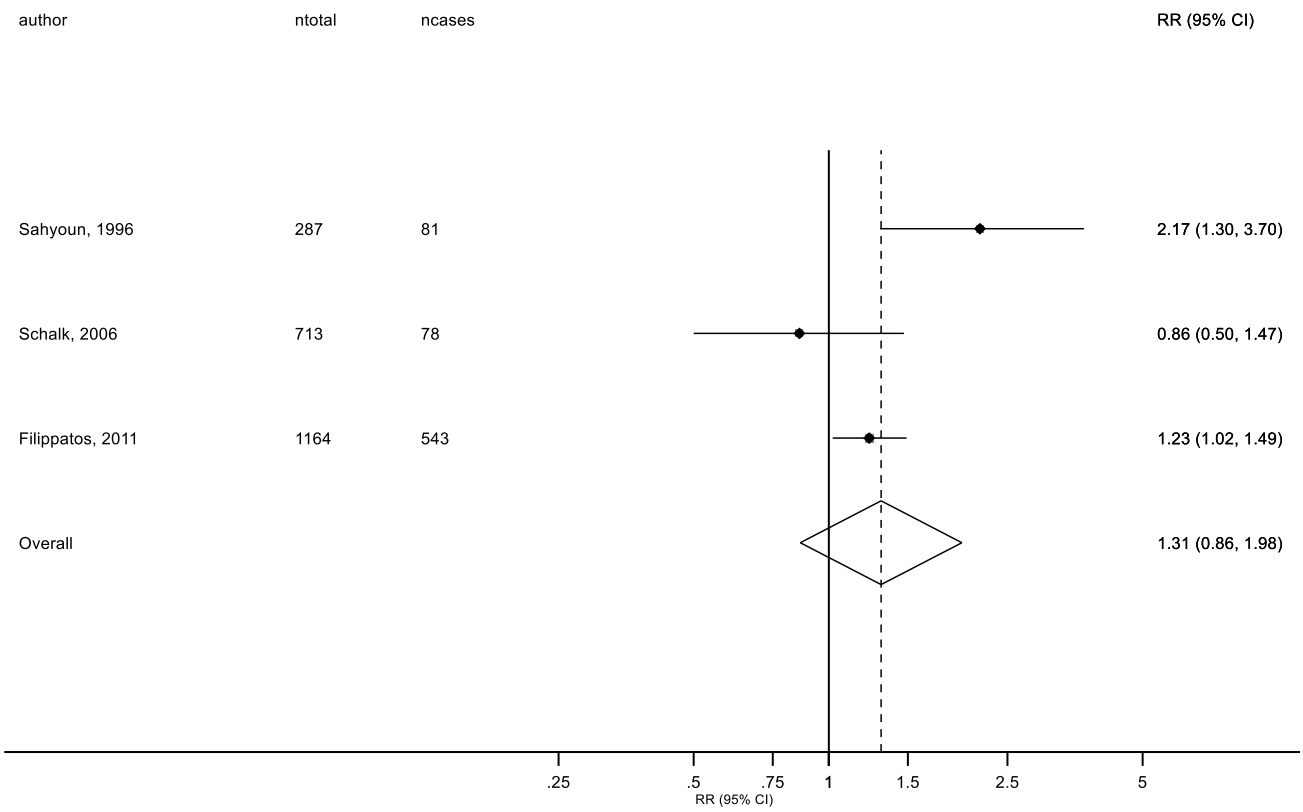
Size of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; RR, relative risk

Supplementary Figure 3: Relative risks for all-cause mortality in individuals in the top versus bottom thirds of baseline levels of serum albumin, grouped according to study level characteristics



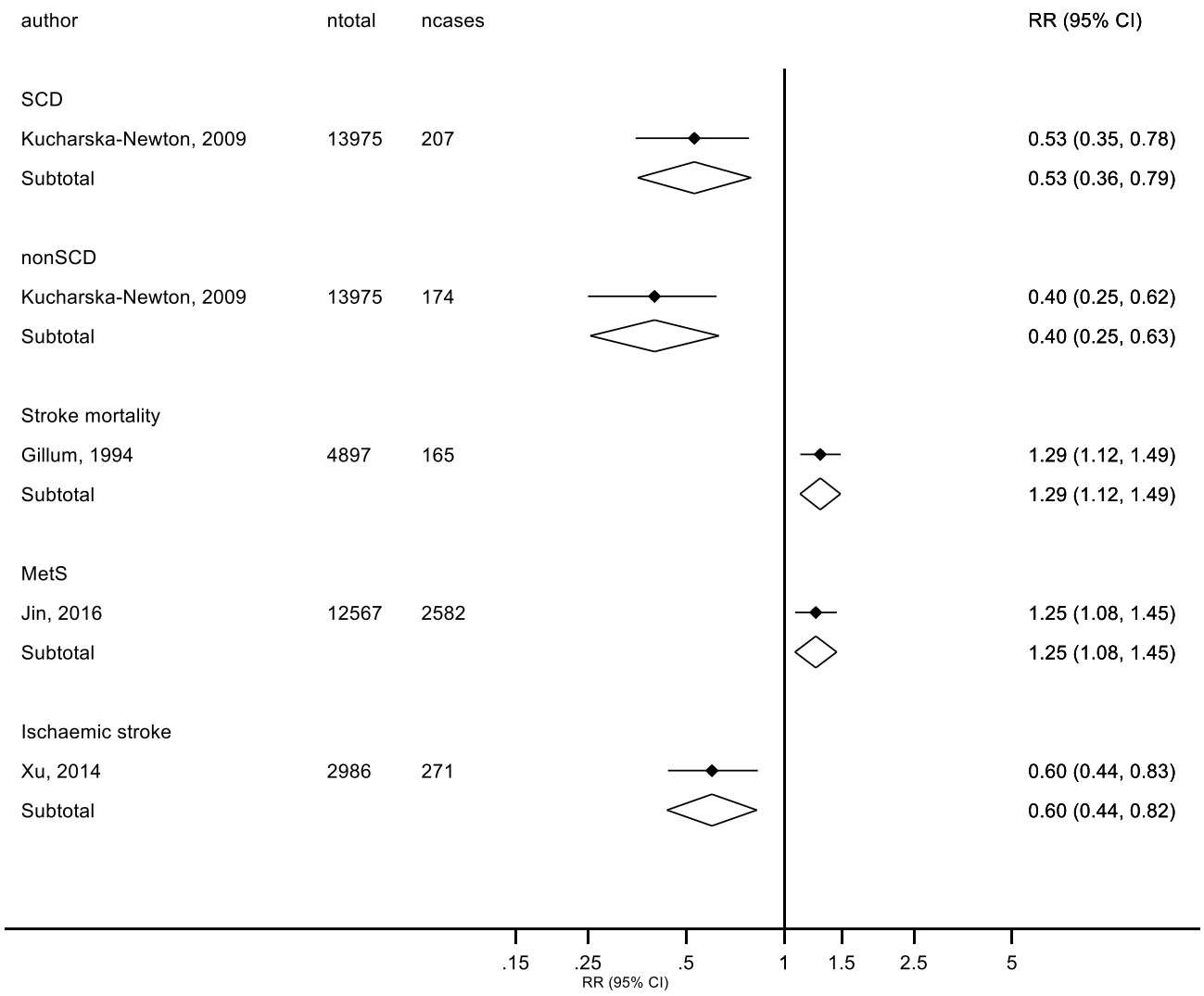
CI, confidence interval (bars); RR, relative risk; *p*-values are for meta-regression

Supplementary Figure 4: Relative risks for all-cause mortality comparing individual with hypoalbuminaemia vs normal albumin



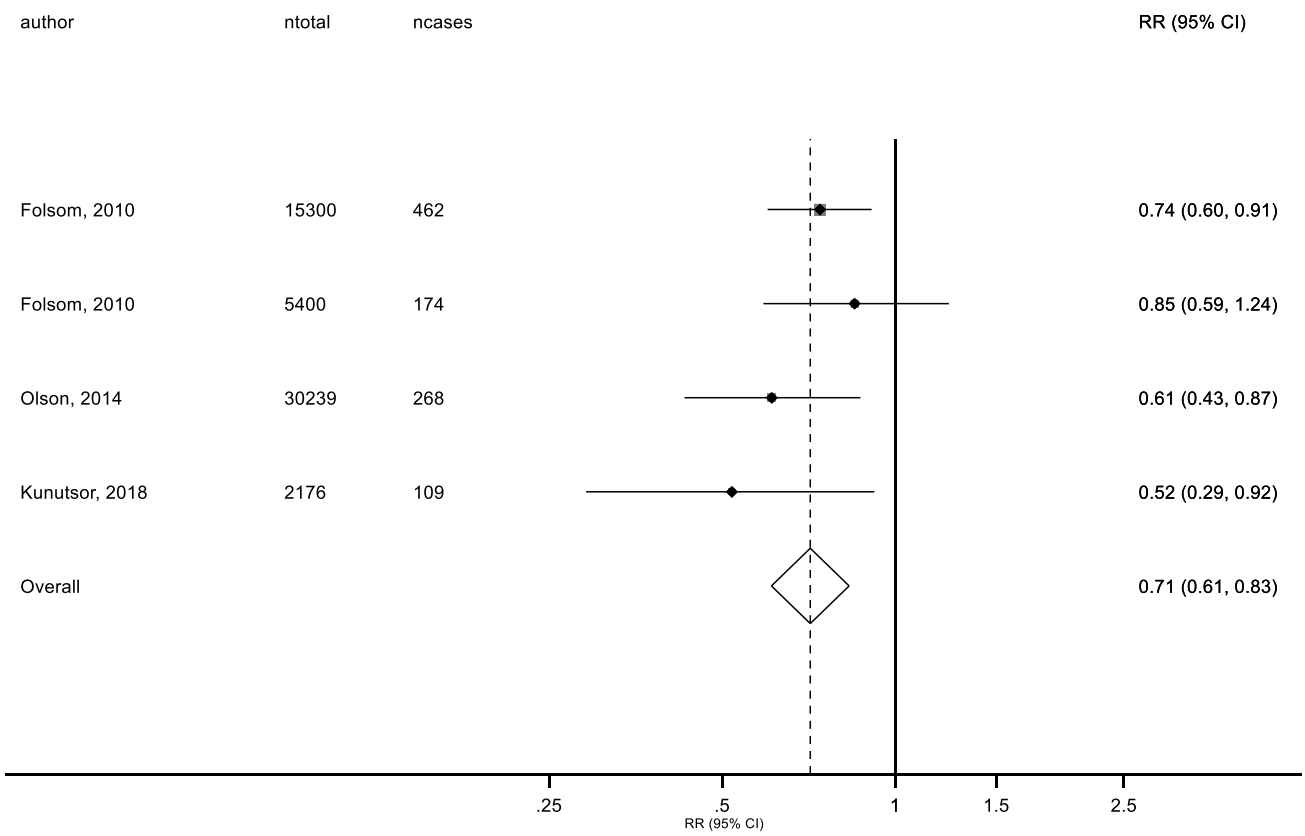
The summary estimates presented were calculated using random effects models; Size of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); RR, relative risk

Supplementary Figure 5: Relative risks for ischemic stroke, stroke mortality, SCD, nonSCD, and MetS in individuals in the top versus bottom thirds of baseline levels of serum albumin



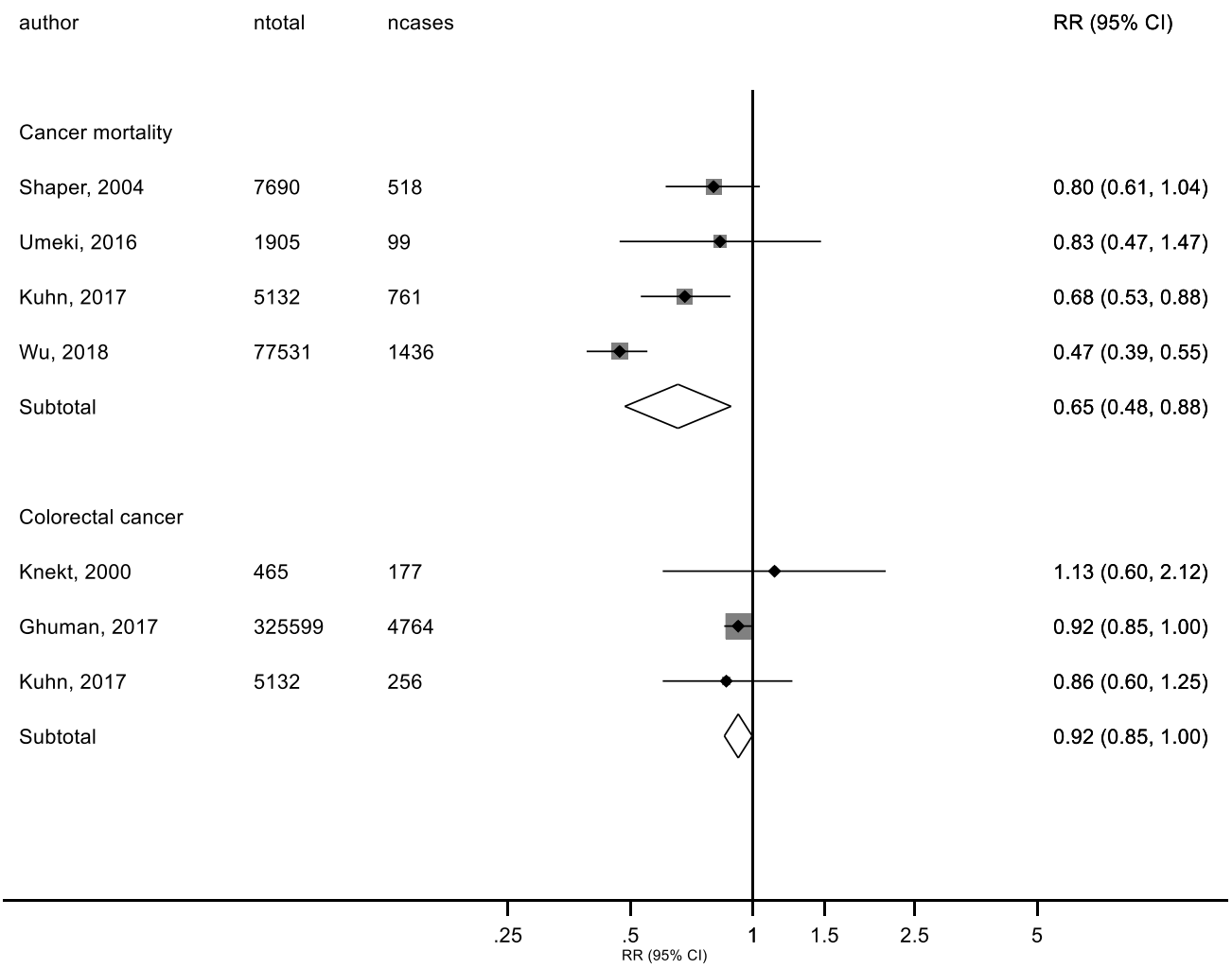
CI, confidence interval (bars); MetS, metabolic syndrome; RR, relative risk; SCD, sudden cardiac death

Supplementary Figure 6: Relative risks for venous thromboembolism in individuals in the top versus bottom thirds of baseline levels of serum albumin



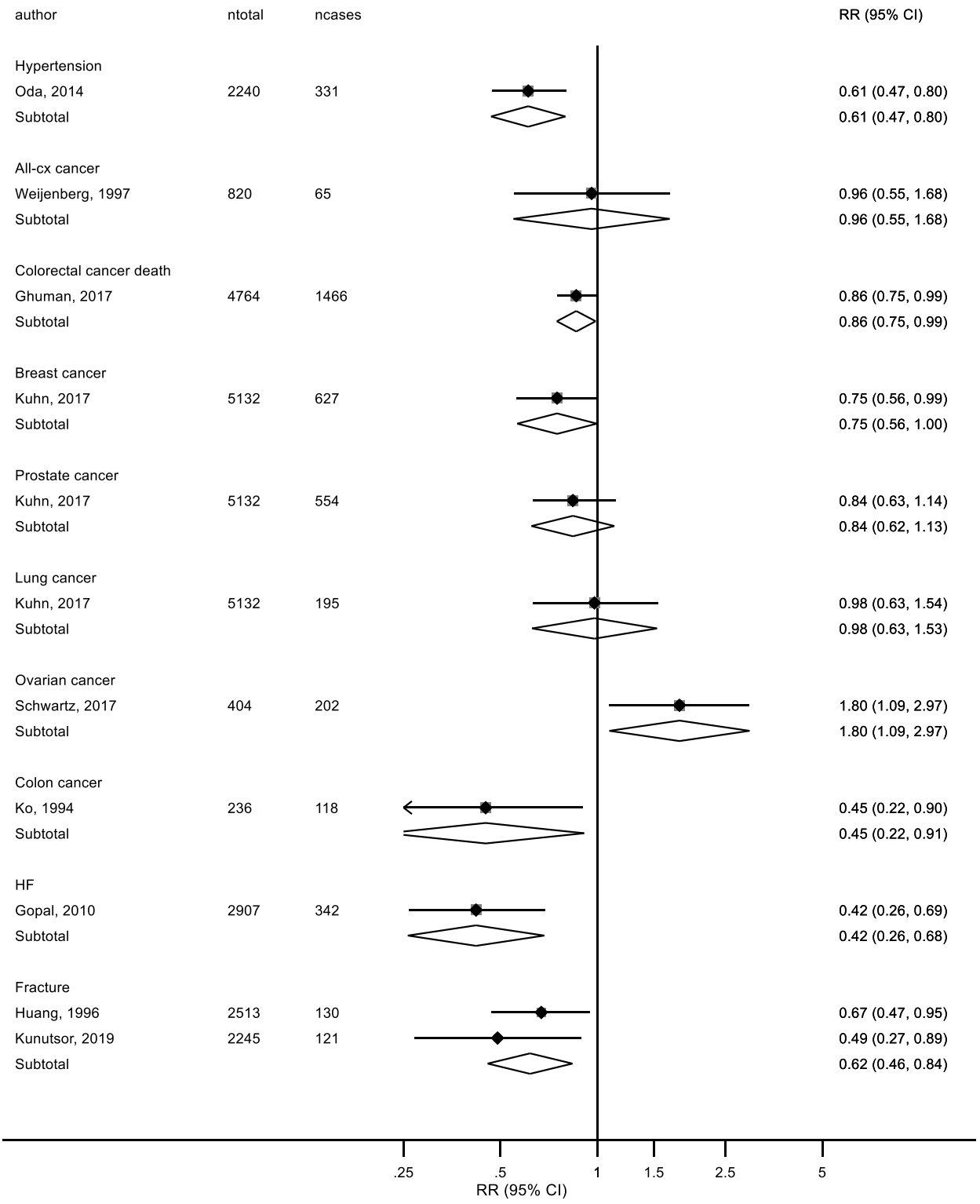
The summary estimates presented were calculated using fixed effects models; Size of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); RR, relative risk

Supplementary Figure 7: Relative risks for cancer endpoints in individuals in the top versus bottom thirds of baseline levels of serum albumin



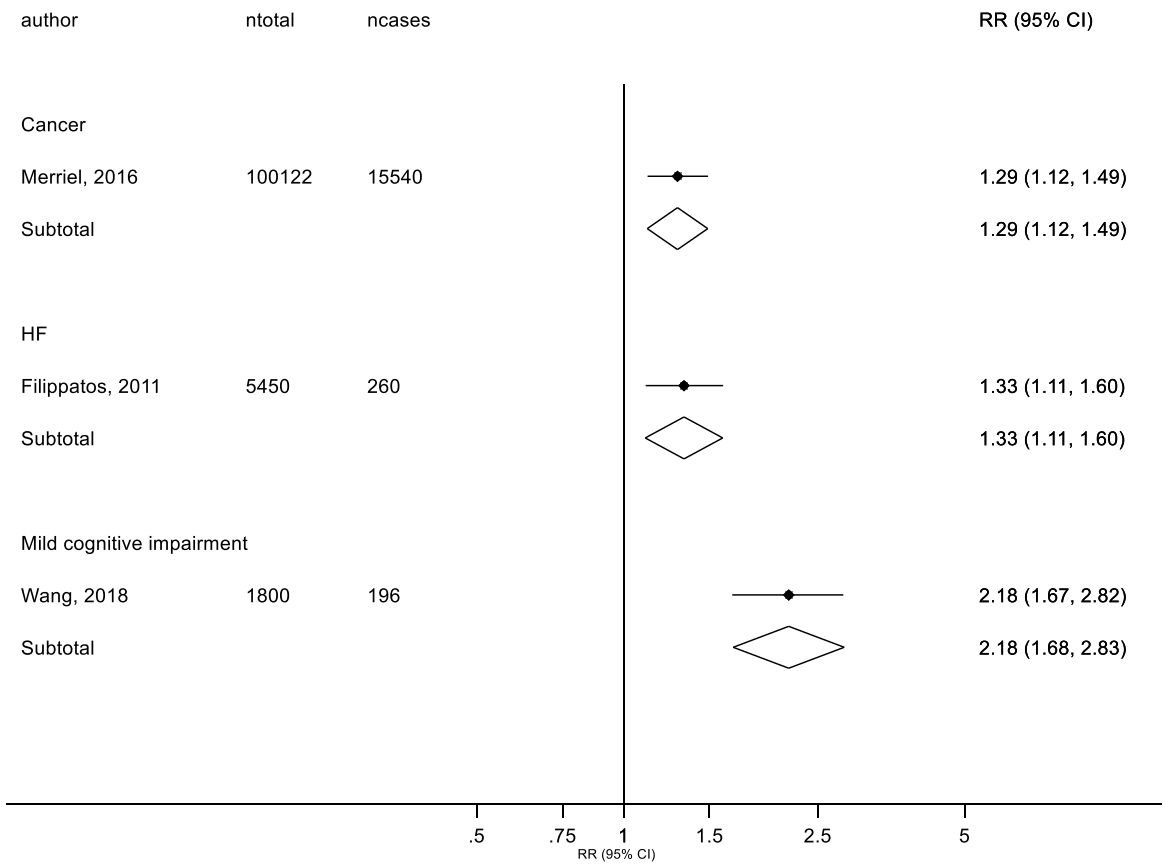
Size of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); RR, relative risk

Supplementary Figure 8: Relative risks for fracture, heart failure, hypertension, breast cancer, colon cancer, ovarian cancer, all-cause cancer, colorectal cancer death, lung cancer, prostate cancer in individuals in the top versus bottom thirds of baseline levels of serum albumin



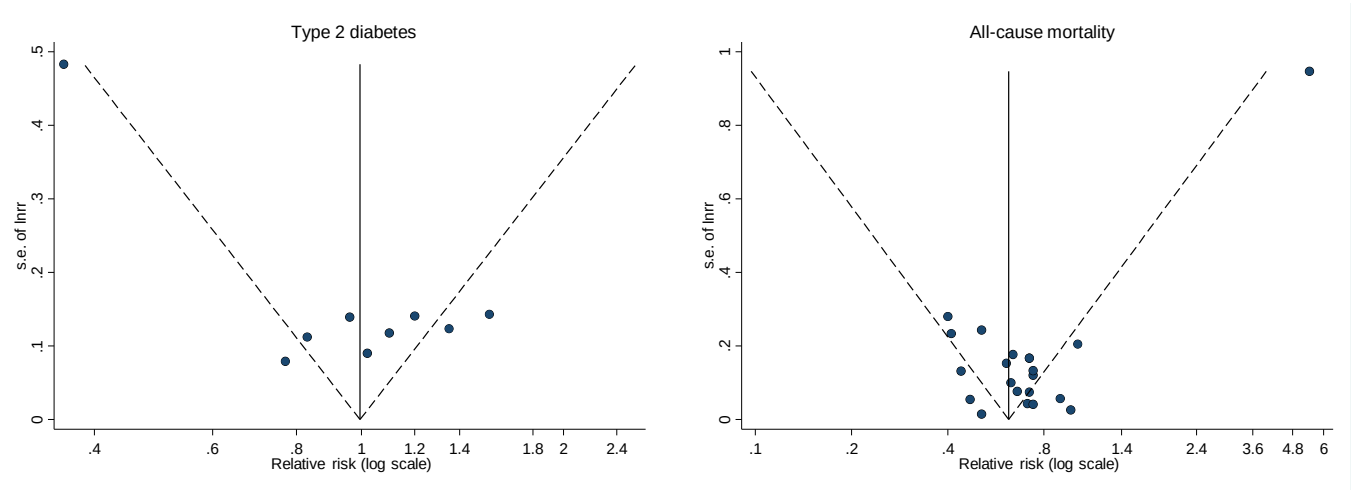
CI, confidence interval (bars); RR, relative risk

Supplementary Figure 9: Relative risks for heart failure, cancer, and mild cognitive impairment comparing individual with hypoalbuminaemia vs normal albumin



CI, confidence interval (bars); HF, heart failure; RR, relative risk

Supplementary Figure 10: Assessment of small study effects by funnel plots and Egger's tests



The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a fixed effect model; *p*-value for bias calculated using Egger's test was 0.72 for type 2 diabetes and 0.34 for all-cause mortality

Table. Baseline characteristics of eligible studies (1990-2020)

Author, year of publication	Study name/source of participants	Country	Baseline year	Study design	Mean/median age or age range (yrs)	Male %	Follow-up (yrs)	Mean albumin (g/l)	Outcome	Nparticipants	Ncases	Confounders adjusted for	Quality score
Darne, 1990	Paris Health Centre	France	1972-1977	Prospective cohort	40-59	66.2	10.5	NR	All-cause mortality	27684	1736	Age and globulin	5
Gillum, 1992	National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS)	USA	1971-1975	Prospective cohort	45-74	NR	15.0	NR	All-cause mortality	5765	2399	Age, smoking, SBP, TC, DM, level of education	8
Klonoff-Cohen, 1992	Rancho Bernardo Heart and Chronic Disease	USA	1984-1987	Prospective cohort	50-89	NR	1.4	42.9	All-cause mortality	2342	83	Age and sex	8
Corti, 1994	Established Populations for Epidemiologic Studies of the Elderly (EPESE)	USA	1981-1983	Prospective cohort	78.7	36.1	3.7	40.5	All-cause mortality	4116	935	Age, race, level of education, disability status, BMI, smoking, chronic conditions	8
Sahyoun, 1996	Nutrition Status Survey	USA	1981-1984	Prospective cohort	74.6	NR	NR	41.5	All-cause mortality	287	81	Age, BUN, TG, history of disease, medical conditions preventing shopping	6
Sahyoun, 1996	Nutrition Status Survey	USA	1981-1984	Prospective cohort	80.7	NR	NR	37.3	All-cause mortality	176	127	Age, BUN, TG, history of disease, medical conditions preventing shopping	5
Huang, 1996	National Health and Nutrition Examination Survey (NHANES I)	USA	1971-1975	Prospective cohort	≥45	0	13.4	NR	All-cause mortality	2513	130	Age, previous fracture hx, menopausal status, physical activity, parity, and alcohol use	8
Weijenberg, 1997	Zutphen Elderly Study	Netherlands	1985	Prospective cohort	71.4	100	5.0	44.1	All-cause mortality	820	189	Age, BMI, DBP, TC, HDL-C, smoking, alcohol consumption, health status	6
Reuben, 2000	Iowa 65+ Rural Health Study	USA	1987-1989	Case cohort	77.5	41.5	4.0	NR	All-cause mortality	632	171	Age, gender, educational level, recent weight loss, body mass index, smoking, myocardial infarction or stroke history, and diabetes history	8
Djousse, 2002	Framingham Offspring	USA	1971	Prospective cohort	37.6	48	21.9	NR	All-cause mortality	4506	499	Age, BMI, TC, HDL-C, alcohol consumption, cigarette smoking, serum bilirubin, and blood pressure	8
Hu, 2003	Mac-Arthur Research Network Study of Successful Aging (substudy of EPESE)	USA	1988	Prospective cohort	74.3	47	7.0	40.9	All-cause mortality	870	197	Age, sex, race, markers of inflammation and undernutrition, history of CAD, hypertension, DM, depression score, smoking status, alcohol consumption, and lipid-lowering medications	8
Shaper, 2004	British Regional Heart Study (BRHS)	UK	1978-1980	Prospective cohort	40-59	100	16.8	44.6	All-cause mortality	7690	1511	Age, smoking, physical activity, social class, BMI, pre-existing CHD/stroke, use of antihypertensive treatment, FEV1, SBP, and TC	7
Ansai, 2007	8020 Data Bank Survey	Japan	1997-1998	Prospective cohort	80.0	39.7	4.0	NR	All-cause mortality	697	108	Gender, smoking status, physical health, status, BMI, TC	7
Okamura, 2008	National Integrated Project for Prospective Observation of Non-communicable Disease	Japan	1980	Prospective cohort	60-74	43.2	12.4	42.6	All-cause mortality	1844	439	Age, TC, DM, hypertension, BMI, smoking, alcohol drinking	7

Author, year of publication	Study name/source of participants	Country	Baseline year	Study design	Mean/median age or age range (yrs)	Male %	Follow-up (yrs)	Mean albumin (g/l)	Outcome	Nparticipants	Ncases	Confounders adjusted for	Quality score
	and Its Trends in the Aged (NIPPON DATA80)												
Carriere, 2008	Pathologies Oculaires Lie´es a` l'Age Study	France	1995-1997	Prospective cohort	70.0	38.4	9.0	41.3	All-cause mortality	1441	221	Age, educational level, perceived health, and smoking	7
Grimm, 2009	General Hospital Vienna	Austria	1992-2002	Prospective cohort	49.9	45	7.4	NR	All-cause mortality	285930	48139	Age and gender	7
Takata, 2012	Niigata City	Japan	1998	Prospective cohort	70.0	50.7	10.0	43.1	All-cause mortality	600	80	Gender, smoking, ADL	7
Sidorenkov, 2012	Northwest Russia	Russia	1999-2000	Prospective cohort	≥18	53.1	10.2	43.4	All-cause mortality	3704	242	Age, education, smoking, frequency of taking >80g alcohol on occasion, physical activity, DBP, ApoB/ApoA1 ratio, BMI, history of CVD	8
Hu, 2013	National Health and Nutrition Examination Survey (NHANES III)	USA	1988-1994	Prospective cohort	47.0	47	13.0	NR	All-cause mortality	18162	4610	Age, sex	8
Hu, 2013	Life Insurance Data	USA		Prospective cohort	42.0	64	4.5	NR	All-cause mortality	311535	837	Age, sex	7
Liu, 2015	Rugao longevity cohort	China	2007-2008	Prospective cohort	97.0	22.2	6.0	42.4	All-cause mortality	433	394	Age, sex, TG, LDL-C, platelet count, lymphocyte count, and neutrophil count	8
Umeki, 2016	Tanushimaru Study	Japan	1999	Prospective cohort	62.6	41.1	15.0	44.0	All-cause mortality	1905	337	Age, sex, HDL-C, LDL-C, TG, eGFR	8
Wu, 2018	Tapei City Geriatric Health Examination Program	Taiwan	2006-2010	Prospective cohort	73.1	50.8	3.3	43.0	All-cause mortality	77531	3840	Age, sex, education level, marital status, BMI, smoking, alcohol consumption, regular exercise, cognitive status, mood disease, eGFR, ALT, anemia, hypertension, DM, hyperlipidemia, CVD, chronic inflammatory diseases, and history of cancer	7
Schalk, 2006	Longitudinal Aging Study Amsterdam (LASA)	Netherlands	1992-1993	Prospective cohort	74.3	NR	6.0	NR	CVD	713	86	Age, sex, education, smoking, alcohol consumption, BMI, PA, DM, DBP, SBP, cognitive impairment, and TC	8
Hayward, 2017	RCGP-RSC database	UK		Prospective cohort	18-90	40.1	9.0		CVD	113993	2369	Multivariate model, but covariates not specified	8
Kuller, 1991	Multiple Risk Factor Intervention Trial (MRFIT)	USA	1973-1976	Nested case control	47.0	100	10.5	45.0	CHD mortality + MI	615	205	Age, DBP, smoking, TC	7
Vazquez-Oliva, 2018	Registre GIronı´ del COR (REGICOR) Study	Spain	2005	Case cohort	55.3	49.8	5.0	42.1	CHD	775	105	Age, sex, smoking, DM, SBP, DBP, TC, and HDL-C	8
Xu, 2014	Northern Manhattan Study	USA	1993-2001	Prospective cohort	69.0	37.2	12.0	44.2	Stroke	2986	329	Age, sex, race-ethnicity, BMI, moderate alcohol drinking, DM, hypercholesterolemia, WBC count, eGFR, and history of AF	8
Gopal, 2010	The Health, Aging, and Body Composition Study **(**Health ABC)	USA	1997-1998	Prospective cohort	73.6	48	9.4	39.8	HF	2907	342	Age, history of CHD, SBP, history of smoking, creatinine, heart rate, fasting glucose, LVH, interleukin-6, CRP, tumor necrosis factor-α, incident CHD	8
Filippatos, 2011	Cardiovascular Health Study (CHS)	USA	1989-1990/1992-1993	Prospective cohort	73.1	42.4	9.6	40.0	HF	5450	260	58 covariates based on sociodemographic characteristics and prevalent medical conditions	9
Oda, 2014	Medical Check-up Center	Japan	2008-2009	Retrospective cohort	49.8	61.8	3.1	43.0	Hypertension	2240	331	sex, age, current smoking, everyday alcohol drinking, BMI, proteinuria,	8

Author, year of publication	Study name/source of participants	Country	Baseline year	Study design	Mean/median age or age range (yrs)	Male %	Follow-up (yrs)	Mean albumin (g/l)	Outcome	Nparticipants	Ncases	Confounders adjusted for	Quality score
												creatinine, uric acid, fasting glucose, log TG, log high-sensitivity CRP, WBC count, hemoglobin, DBP	
Stranges, 2008	Western New York Study (WNYS)	US	1996-2001	Prospective cohort	59.0	52.5	5.9	43.4	Type 2 diabetes	219	61	Age, family history of diabetes, smoking, drinking status, and BMI	7
Abbasi, 2012	European Prospective Investigation Into Cancer and Nutrition (EPIC)-Netherlands	the Netherlands	1993-1997	Prospective cohort	49.1	25.7	10.2	38.9	Type 2 diabetes	38379	924	age, DM risk factors	9
Abbasi, 2012	Prevention of Renal and Vascular End-stage Disease (PREVEND)	the Netherlands	1997-1998	Prospective cohort	48.9	49.1	7.7	45.8	Type 2 diabetes	7952	503	age, DM risk factors	9
Bae, 2013	Total Healthcare Center	Korea	2005-2009	Prospective cohort	44.6	73.7	4.0	45.5	Type 2 diabetes	9029	556	Age, triglyceride, HDL-C, LDL-C, SBP, BMI, presence of IFG and fatty liver, smoking status, and alcohol consumption.	8
Liu, 2017	Chinese PLA general hospital	China	2009-2013	Retrospective cohort	71.0	100	4.0	44.3	Type 2 diabetes	18384	450	Age, marital status, current smoking, current alcohol drinking, BMI, baseline FPG, baseline 2hPG, baseline eGFR, baseline prevalence and treatment status of hypertension and dyslipidemia	6
Hwang, 2018	Health Promotion Center of Samsung Medical Center	Korea	2006-2012	Retrospective cohort	51.0	56.8	5.0	NR	Type 2 diabetes	15428	599	Age, sex, BMI, smoking status, SBP, FPG, HbA1c, TG, LDL-C, HDL-C, CRP, percent body weight change, serum insulin	8
Hu, 2020	Xiaotangshan hospital in Beijing	China	2009-2016	Prospective cohort	41.0	57.9	3.0	44.9	Type 2 diabetes	30442	1634	Age, sex, heart rate, systolic blood pressure and levels of serum uric acid, TC, TG, HDL-C and ALT, white cell count, eGFR, FPG, BMI	8
Folsom, 2010	Atherosclerosis Risk in Communities (ARIC)	USA	1987-1989	Prospective cohort	54.2	45.1	16.9	38.7	VTE	15300	462	Age, sex, race, HRT use, race, diabetes status, history of cancer, eGFR, BMI, factor VIII, aPTT, fibrinogen	9
Olson, 2014	REasons for Geographic And Racial Differences in Stroke (REGARDS)	USA	2003-2007	Prospective cohort	≥45	NR	4.6	42.0	VTE	30239	268	Age, sex, race, region, race*region interaction, BMI, smoking, hypertension, DM, history of CHD or stroke	8
Ko, 1994	Washington County	USA	1974	Nested case control	NR	34.7	NR	41.3	Colon cancer	236	118	Age, sex	6
Knekt, 2000	Finnish Mobile Clinic	Finland	1968-1972	Nested case control	53.6	46.3	23.0	46.3	Colorectal cancer	465	177	Age, sex, municipality	8
Merriel, 2016	Clinical Practice Research Datalink (CPRD)	UK	2003-2007	Prospective cohort	76.5	48.6	1.0	41.2	Cancer	100122	15540	Age, gender and history of chest/abdominal trauma, sepsis, liver failure, HF or nephrotic syndrome	5
Ghuman, 2017	Apolipoprotein Mortality Risk Study (AMORIS)	Sweden	1986-1999	Prospective cohort	45.8	NR	18.0	43.3	Colorectal cancer death	325599	4764	Age, sex, education, SES, Charlson comorbidity index, UC, glucose, TC and TG	8

Author, year of publication	Study name/source of participants	Country	Baseline year	Study design	Mean/median age or age range (yrs)	Male %	Follow-up (yrs)	Mean albumin (g/l)	Outcome	Nparticipants	Ncases	Confounders adjusted for	Quality score
Kuhn, 2017	European Prospective Investigation Into Cancer and Nutrition (EPIC)-Heidelberg	Germany	1994-1998	Case cohort	52.6	46.5	11.8	46.0	Cancer mortality	5132	761	Age, smoking, alcohol intake, current aspirin use, physical activity, WC, BMI, height, education level	9
Schwartz, 2017	Janus Serum Bank Cohort	Norway	1978-2004	Nested case control	42.6		28.5	51.0	Ovarian cancer	404	202	Age, height, BMI	8
Wang, 2018	Tianjin Medical University General Hospital	China	2008-2009	Retrospective cohort	72.1	75.4	7.0	44.1	Mild cognitive impairment	1800	196	Sex, age, race, BMI, medical history, medicine history, CRP, uric acid and total bilirubin	7
Kunutsor, 2019	Kuopio Ischemic Heart Disease (KHID)	Finland	1984-1989	Prospective cohort	53.0	100	25.6	42.3	Fracture	2245	121	Age, BMI, SBP, history of hypertension, prevalent CHD, smoking, physical activity, history of T2D, eGFR, SES, dietary energy intake, serum ionized calcium, CRP	8

AF, atrial fibrillation; ApoB, apolipoprotein B; ApoA1, Apolipoprotein A1; aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; HF, heart failure; IFG, impaired fasting glucose; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; PA, physical activity; SES, socioeconomic status; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides; UC, ulcerative colitis; WBC, white blood cell; VTE, venous thromboembolism; WC, waist circumference